1.0 SCIENTIFIC ABSTRACT

About 164,100 new cases of non-small cell lung cancer (NSCLC) were diagnosed in the U.S. in 2000. Forty percent of these are candidates for surgical resection with curative intent. About 25% have locally advanced, non-metastatic disease and are not candidates for resection. In these patients, thoracic radiation leads to a median survival of 9-12 months. The addition of platinum-based combination chemotherapy before or after thoracic radiation extends survival over radiation alone. Recent single-arm trials demonstrate the feasibility of administering platinum-based regimens concurrently with radiation and suggest the possibility of improved survival. Weekly carboplatin 100 mg/m^2 plus paclitaxel 45 mg/m^2 given simultaneously with 65 Gy thoracic radiation to 38 patients has been shown to lead to a three year actuarial survival of 54% (95% confidence interval 35-70%)[1]. Such concurrent chemoradiation approaches are currently being evaluated in randomized trials.

Esophagitis is the principal dose-limiting toxicity observed in chemoradiation trials. Techniques such as conformal radiotherapy, alteration in treatment fractionation and administration of radioprotective agents attempt to limit this toxicity but have met with only limited success and carry the risk of reducing the effective radiation dose to the lung tumor. New methods of effectively protecting the esophagus would reduce treatment-related morbidity, potentially increase the deliverable radiation dose, and lead to better disease control.

Esophageal damage in response to ionizing radiation results from the local production of toxic free radical species. Enzymatic oxidation of these species protects cells from excessive free radical-induced damage. Manganese Super Oxide Dismutase (MnSOD) is a principal mediator of this protective effect. Delivery of the MnSOD gene to esophageal tissues and consequent local overexpression of MnSOD may increase esophageal resistance to radiation without compromising therapeutic efficacy.

[1] Belani et al. Proc. Amer. Soc. Clin. Oncol 16; 448a, 1997

Cationic liposomes comprising human MnSOD-encoding plasmid carrying an *SOD-2* cDNA have been administered to mice receiving esophageal radiation. Intraesophageal administration of MnSOD plasmid/lipid leads to MnSOD mRNA and protein expression in esophageal mucosa. Gene therapy-mediated overexpression MnSOD decreases the expression of inflammatory cytokines in response to radiation and reduces cellular apoptosis, micro-ulceration and esophagitis. These findings support an attempt to reduce esophageal toxicity by delivering MnSOD plasmid/lipid to patients receiving combination chemoradiation.

A clinical trial has been designed to test the hypothesis that plasmid-based delivery of the gene for MnSOD can reduce esophageal toxicity secondary to 65 Gy radiation therapy given concurrently with weekly carboplatin (AUC = 2) plus paclitaxel (45 mg/m^2). Patients will receive two doses of MnSOD plasmid/lipid liposomes by swallowing on days 1 and 3 of each weekly chemotherapy/radiation cycle. A dose escalation phase will rule out excessive toxicity of the plasmid-lipid complex and define a maximum tolerated dose. An expanded cohort of patients will be treated at the maximum tolerated dose and the incidence of esophagitis will be assessed. This part of the trial will provide an estimate of the ability of MnSOD plasmid/lipid to reduce the expected incidence of esophagitis in this group.